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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a r quest for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Bernard H.	Weigle	Seattle, Washington, USA
Ron L.	Bardell	Seattle, Washington, USA

☐ *Additional inventors are being named on the _____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

METHOD AND APPARATUS FOR MODELING OF MICROSALE PROCESSES TO SPEED DEVELOPMENT AND ENHANCE PERFORMANCE OF A MEDICAL DIAGNOSTIC DEVICE

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Address	275 Middlefield Road				
Address					
City	Menlo Park	State	CA	ZIP	94025-3506
Country		Telephone		Fax	

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☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE _____

TYPED or PRINTED NAME Hao Y. Tung

TELEPHONE (650) 324-7000

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

Attorney Docket No.: 38187-2695

PROVISIONAL PATENT APPLICATION

METHOD AND APPARATUS FOR MODELING OF MICROSCALE PROCESSES TO SPEED DEVELOPMENT AND ENHANCE PERFORMANCE OF A MEDICAL DIAGNOSTIC DEVICE

Inventor(s):

BERNHARD H WEIGL
Seattle, Washington 98103

RON L BARDELL
Seattle, Washington 98103

Assignee:

Pelikan Technologies, Inc.
1072 East Meadow Circle
Palo Alto, California 94303

Status: Small Entity

HELLER EHRMAN WHITE & MCAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025-3506
(650) 324-7000

PATENT

Attorney Docket No.: 38187-2695

METHOD AND APPARATUS FOR MODELING OF MICROSCALE PROCESSES TO SPEED DEVELOPMENT AND ENHANCE PERFORMANCE OF A MEDICAL DIAGNOSTIC DEVICE

BACKGROUND OF THE INVENTION

The technical field relates to design of diagnostic devices such as but not limited to micro analytical devices.

Significant advances have been made in the development of microscale fluid handling technologies for medical diagnostic applications. In 2001, Larry Kricka of the University of Pennsylvania surveyed the range of micro analytical devices, from microfluidic chips and gene chips to bioelectronics chips, and their impact on diagnostic testing[1]. He predicted a move of clinical testing from central laboratory to non-laboratory settings with a positive impact on healthcare costs. MIT Technology Review named microfluidics one of ten technologies that will change the world[2] and one of the many areas in which this will be seen is in the in-vitro-diagnostics sector.

With macroscopic devices, such as conventional blood chemistry analyzers or flow cytometers, it is usually possible during the development phase to mount flow sensors, temperature probes, and optical detectors at various positions along the instrument pathway to experimentally determine the optimum operational parameters for the device. However, this approach often fails for microdevices because standard sensors and probes are typically of the same scale as the microdevice and interfere so much with device behavior that the measured data do not represent actual device performance. Thus, the most useful experimental data tend to be external measurements from which the internal physics of the microdevice should be deduced.

SUMMARY OF THE INVENTION

The present invention provides solutions for at least some of the drawbacks discussed above. The technical field methods for designing microscale devices. Because the difficulty of building such sensors for testing, the ability of the present invention to accurately model the microscale device is of interest. Specifically, some embodiments of

the present invention provide an improved method and model for developing such microscale devices. At least some of these and other objectives described herein will be met by embodiments of the present invention.

The invention disclosed here comprises the use of a mathematical modeling algorithm to develop a list of design rules for dispersed-phase-based biosensors. Furthermore, various pieces of hardware as well as embodiments of a glucose sensor are disclosed.

A further understanding of the nature and advantages of the invention will become apparent by reference to the remaining portions of the specification and drawings.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The present invention provides a solution for body fluid sampling. Specifically, some embodiments of the present invention provides a method for improving spontaneous blood generation. Because the penetration distance is a strong predictor of the success of the lancing event for spontaneous blood generation, the ability of the device to accurately control this distance is of interest. For some embodiments of penetrating member drivers, the invention provides improved methods for controlling the velocity and cutting efficient of a penetrating member. At least some of these and other objectives described herein will be met by embodiments of the present invention.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. It may be noted that, as used in the specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a material" may include mixtures of materials, reference to "a chamber" may include multiple chambers, and the like. References cited herein are hereby incorporated by reference in their entirety, except to the extent that they conflict with teachings explicitly set forth in this specification.

In this specification and in the claims which follow, reference will be made to a number of terms which shall be defined to have the following meanings:

"Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not. For example, if a device optionally contains a feature for analyzing a blood sample, this means that the analysis feature may or may not

be present, and, thus, the description includes structures wherein a device possesses the analysis feature and structures wherein the analysis feature is not present.

I. Introduction

Mathematical modeling of microscale processes is a uniquely useful alternative to the known approaches since the chemical and physical processes in the microscale generally follow deterministic physical laws that can be accurately represented in mathematical models. Once validated by external measurements, modeling can predict internal behavior at any point in space and time within the microdevice, leading to new insights and optimization techniques, e.g., the accurate fitting of non-linear response functions, optimization of system dynamics, or location of a specific region of incomplete reagent mixing, complete with design modifications that will remedy the problem.

Many developers of microdevices utilize this very powerful approach of simultaneous modeling and experimentation. Microscale fluid movers have been developed using both linear[3-5] and nonlinear[6-8] modeling, even when complex fluids such as particle suspensions[10,11] are involved. Other components of microfluidic systems[12-17] have benefited from this dual approach as well.

The large surface-to-volume ratio characteristic of microdevices, however, frequently leads to unexpected behaviors. For example, microvolumes of physiological fluids evaporate, cool, and heat extremely rapidly and modeling is often desirable to accommodate, or leverage, such heat transfer and evaporation processes and their impact on the system. At the typical low Reynolds-number (slow flows) in microdevices, mixing is often problematic and modeling guides the design to achieve mixing requirements.

The modeling of laminar flow is rarely an end in itself, but since the exact governing equations can be solved analytically in simple channels, or numerically in more complex channels, this produces valuable knowledge of the flowfield and its effect on other important physical processes, for example the precise control of chemical reaction rate by designing the diffusive mixing of the reactants. A multiphysics model is the result and is extremely useful to experimentalists tasked with sorting out the effects of a microdevice with complex physics. Many researchers have utilized this approach to develop devices for fluid constituent extraction[18], property measurement such as pH[19],

viscosity[20], and diffusion coefficient[21], quantitative analysis[22], sample preparation[23], and laminate-based microfluidic devices for biomedical applications[24-28].

To illustrate how modeling can speed the development of diagnostic products we relate our experience of using one embodiment of the present invention to model a microscale processes to speed development of a microfabricated glucose sensor.

II. The modeled system as example – a microfabricated glucose sensor as part of a novel blood collection device with integrated lancet.

Referring now to Figure 1, effort has been made to develop a novel microfabricated point-of-use glucose sensor to be integrated within an automated low-volume lancet-based blood collection device. In one embodiment, the blood collection device is optimized to achieve almost painless blood acquisition of approximately 200 nL per sample (1/100th of a drop of blood). It should be understood, of course, that other volumes such as about 500nl, 400nl, 300nl or less can also be used in other embodiments of the invention. A new integrated glucose sensor was developed to be compatible with such small fluid volumes, as well as, for example and not limitation, a sub-10 second response time and an accuracy of ± 5% over the clinical range. Figure 1 shows one embodiment of the prototype sensor arrangement as well as the integrated glucose lancing device. The analyte detecting members may be clustered in units of five for each sample measurement and within a microchannel along which a blood sample flows.

Figure 1

We focus here on the analyte detecting member itself, a new type of fluorescence-optical glucose biosensor. In one embodiment, the membrane comprises an emulsion that incorporates the enzyme glucose oxidase (GOX) to catalytically consume sample glucose and co-consume oxygen. The emulsion additionally contains an oxygen-quenchable fluorescent indicator that determines the concentration, and hence consumption, of oxygen within the analyte detecting member by a change in fluorescence and thus is related to the sample glucose concentration. The indicator is contained in dispersed hydrophobic droplets within a hydrophilic matrix containing GOX. The use of an emulsion enables single-step deposition of the analyte detecting member, avoiding much complexity in manufacturing and maintains optimal micro-environments for the GOX and

the fluorescent indicator. Other significant advantages such as faster response times are expected.

The analyte detecting member model mathematically replicates the significant physical and chemical processes taking place in the analyte detecting member and sample. Figure 2 provides a simplified schematic of the most important processes.

Figure 2

Prior to contact between the sample and the analyte detecting member layers, the whole blood sample contains red blood cells (RBCs) at a given hematocrit level and plasma with dissolved oxygen (bound to hemoglobin inside the RBCs and equilibrated with the surrounding plasma), human catalase (with no significant exchange of catalase between RBCs and plasma), glucose (which is the analyte), and hydrogen peroxide. In this embodiment, the sample is assumed to contain no GOX at this point. Other blood constituents that diffuse into the analyte detecting member layer are not expected to have a significant impact on the analyte detecting member chemistry at the concentrations they can reach within 60 seconds after exposure.

Prior to sample contact, the analyte detecting member membrane (dispersed-phase) contains a fluorescent indicator in the form of a ruthenium complex immobilized within microdroplets of a hydrophobic material (a siloxane-containing polymer) that are of known concentration and size distribution and embedded in a continuous hydrogel matrix of known water, polymer, and GOX content (see photo in Figure 2). The membrane additionally has an oxygen concentration in equilibrium with the atmosphere.

When the analyte detecting member is initially exposed to the sample, the diffusion of all species is affected by the presence of the dispersed hydrophobic droplets; depending on the diffusion and partition coefficient of the each diffusing species, their diffusion rate may be increased or decreased. GOX starts to diffuse out of the analyte detecting member and into the sample at a slower rate than that of the small diffusants. As the glucose molecules reach the GOX molecules, they are metabolized and converted, with the co-consumption of oxygen and production of hydrogen peroxide, to gluconic acid, which in turn is instantaneously and non-reversibly hydrolyzed to gluconolactone.

The ruthenium complex (ruthenium-diphenylphenantroline $Ru(dpp)_3^{2+}$) in the hydrophobic microdroplets is initially in equilibrium with the ambient oxygen

concentration, and its fluorescent lifetime is quenched to some degree. As oxygen is consumed by the GOX enzyme reaction a concentration gradient is generated between the hydrophobic microdroplets and the surrounding hydrogel, causing the diffusion of oxygen out of the microdroplets. At the same time, oxygen from the plasma in the sample (continually replenished by the RBCs) is diffusing into the analyte detecting member and locally counteracting the reduction in oxygen concentration accomplished by the GOX enzyme reaction. The net effect is a location-dependent reduction in the oxygen concentration in the microdroplets. The dispersed ruthenium complex within the microroplets is thus quenched to a value somewhere between the values for ambient and for about 0 mbar oxygen. Fluorescence lifetimes for these systems tend to be in the low microsecond range.

Modeling Methodology

The analyte detecting member model mathematically implements the physics of the analyte detecting member as described above. It divides the assay time into small time steps and the analyte detecting member into small control volumes. In the current embodiment, during each time step (and in each control volume), the model simultaneously solves a specie conservation equation for each important constituent: oxygen, glucose, glucose oxidase, catalase, and hydrogen peroxide. Each conservation equation includes an accumulation term, a diffusion term, and a production/destruction term. The latter relies on a production rate calculated either as a Michaelis-Menton reaction (catalase) or Ping-Pong Bi-Bi reaction (glucose oxidase).

The analyte detecting member model may track the diffusion of each important chemical component of the emulsion and sample, the chemical reactions between them, and the resulting signal from oxygen depletion. When the oxygen mass transfer rate between the hydrophobic droplet and surrounding hydrogel is as fast as the mass transfer rate of oxygen and glucose in the hydrophilic phase by diffusion, the concentration of oxygen in a droplet and the surrounding hydrophilic phase will always be close to equilibrium. This depends mainly on droplet diameter and diffusion coefficients, and is true for this analyte detecting member emulsion when the droplets are less than 5 microns in diameter. This rapid equilibration allows a welcome simplification in that the emulsion can be considered a single continuous material with averaged properties, instead of two

segregated materials, one for each phase, requiring constant updating of the local oxygen flux between them.

Thus, the analyte detecting member model treats the emulsion as a continuum with properties based on volume-fraction averages of the properties of the hydrophobic and hydrophilic phases. The volume-averaged properties include: diffusion coefficient, solubility, and initial concentrations of each conserved chemical species. Using oxygen concentration in the analyte detecting member membrane as an example, the initial concentration (mM) is

$$[O_2] = f_{Aq} S_{O2\,Aq} + f_{Si} S_{O2\,Si},$$

the effective partition coefficient is

$$H_{O2} = f_{Aq} + f_{Si} \frac{S_{O2\,Si}}{S_{O2\,Aq}},$$

and the diffusion coefficient

$$D_{O2} = f_{Aq} D_{O2\,Aq} + f_{Poly} (1 - f_{Si}) D_{O2\,Poly} + f_{Si} D_{O2\,Si}$$

where f_{Si} is the volume fraction of the emulsion that is hydrophobic phase, f_{Aq} and f_{Poly} are the volume fractions of the hydrophilic phase that are aqueous and polymer, respectively. The diffusion coefficients of oxygen in water, hydrogel polymer, and hydrophobic phase are $D_{O2\,Aq}$, $D_{O2\,Poly}$, and $D_{O2\,Si}$. Finally, the solubilities of oxygen in water and hydrophobic phase at initial conditions are $S_{O2\,Aq}$ and $S_{O2\,Si}$ in mM units.

Solution of each constituent's conservation equation, each impacted by chemical reactions with other constituents, produces the predicted concentrations of oxygen, glucose, glucose oxidase, catalase, and hydrogen peroxide at every location in the analyte detecting member membrane and sample, as shown in the Figures 3 to 7.

III. Results from Model and Experiment

The following sets of plots illustrate some of the information generated by the model and the corresponding experiment for one set of initial conditions and analyte detecting member parameters. In these plots we used glucose-loaded saline solutions to provide tightly-controlled samples.

Enzyme reaction rates (in mM/s):

Figure 3

Figure *3a* shows the reaction rate for *catalase from Aspergillus niger* (as contaminant of GOX) and, in Figure *3b*, *glucose oxidase from Aspergillus niger* as a function of cross-sectional distance through the sample (1 mm on the left) and analyte detecting member (0.047 mm). The curves correspond to 5, 10, 15, and 20 seconds after the exposure of the analyte detecting member membrane to the sample. Both reactions occur almost solely in the analyte detecting member; their initial rates are the highest.

Concentrations profile of enzymes (in mM):

Figure 4

Figure 4 shows the *concentration of glucose oxidase from Aspergillus niger* (*4a*), and *concentration of catalase from Aspergillus niger* (as contaminant of GOX) (*4b*) across a sample and analyte detecting member cross section. Experiments have shown that the A. niger enzymes are somewhat immobilized in the analyte detecting member emulsion by an as yet unknown mechanism (possibly entrapment), diffusing approximately 10^3 times more slowly than if free. This reduction is implemented in the model, which only allows the normal diffusion speed in the sample.

Concentrations of reactants (in mM):

Figure 5c

Figure 5 shows the *concentrations of the reactants*: oxygen, freely dissolved in sample and analyte detecting member emulsion (5a), and hydrogen peroxide (5b) and glucose (5c), both freely dissolved in sample and analyte detecting member hydrophilic phase. These concentrations are affected by *both* diffusion and the consumption / production by chemical reactions over time. The decrease in oxygen concentration in the hydrophobic phase is the cause of the change in fluorescence lifetime. Figure 5b shows an increase in hydrogen peroxide concentration produced by the glucose oxidase activity; hydrogen peroxide that diffuses into the sample largely escapes the catalase reaction.

Fluorescence lifetimes:

Figure 7

Figures 7a and 7b shows the *simulated dynamic response* of a analyte detecting member with good overall response characteristics: fast response, dynamic range in the

physiologically important range, and a large enough signal change to be useful. The analyte detecting member has a hydrophobic to hydrophilic volume fraction of 40/60, an overall thickness of 47 micrometers, and 70% water in the hydrophilic phase.

Figure 7a shows a simulated calibration graph, plotted for different times after initial analyte detecting member exposure. The analyte detecting member shows a solid response over the whole glucose range in less than 10 seconds. Figure 7b shows simulated response curves, plotted for different glucose concentrations. The analyte detecting member reaches a plateau for the high glucose level after less than 10 seconds, while the medium and low glucose levels show an acceptable response over a similar time (in kinetic measurement mode). For reference, the normal range of glucose concentration in capillary blood is 3.5-6 mM. The 25 mM case represents an extremely high, critical glucose level. In Figure 7b, the signal for even the high glucose level never reaches a signal of 100%, which would be equivalent to complete consumption of all oxygen present in the analyte detecting member, but rather a steady state value above 95%. The discrepancy is due to oxygen diffusion from the sample. The fact that oxygen diffusion is relatively minor is advantageous as the analyte detecting member will not be significantly sensitive to variations in oxygen concentrations in the sample.

Figure 8 shows *test data* taken with a prototype analyte detecting member membrane using the same initial conditions and analyte detecting member parameters as supplied to the analyte detecting member model for the preceding figures. The predicted response (Figure 7b) agrees with the test data, especially at the higher glucose loading. The data from the prototype membrane displays some variability and a slightly reduced dynamic range compared to that predicted.

1.FIGURE 8

IV. Discussion and Conclusions

In only a few months this project proceeded from an abstract concept to working prototypes of a distinctly new type of glucose analyte detecting member composed of a novel emulsion-based sensing layer. One reason for this success is the excellent coordination between the experimental teams and the modelers, who worked synchronously on physical prototypes and mathematical modeling, utilizing the same proposed analyte detecting member parameters and test conditions. This strengthened the

modeling by providing experimental validation and strengthened the experimental effort as the model identified anomolous test results before the testing effort could veer off course. The design envelope is more quickly explored by feeding variations from tested conditions to the model, thus adding additional value to the experimental results. The following are concrete examples of this efficient coordination of experimental and modeling work.

The model was instrumental in the beginning of the development project to predict that rapid (sub-10 second) response was indeed possible (at a time when the experiments still showed response time of minutes due to material incompatibilities that were later corrected).

It was also discovered through modeling that GOX activity at concentrations higher than 3-5 mM in the analyte detecting member layer were highly non-linear, and that there was an inhibitory effect on GOX activity at those concentrations. This freed the experimental teams from trying to push the GOX concentration in the analyte detecting member to the solubility limit.

For manufacturing purposes, in some embodiments, the analyte detecting members were designed so that were less than 50 micrometers thin. The model, however, had predicted an optimum balance between response time and cross-sensitivity to sample oxygen for a analyte detecting member of approximately 100 micrometers thickness. It should be understood, of course, that various thicknesses may be used with different devices without deviating from the scope of the invention. So the model was exercised repeatedly to explore the design space; it predicted that if the GOX concentration was changed to 3 mM it would be possible to achieve a similar balance between fast response time, good dynamic range, and low cross sensivity.

A particularly puzzling phenomenon was discovered when the experimental teams noticed a significant drop-off of glucose signal (an increase in fluorescence lifetime, or more accurately, in hybrid fluorescence phosphorescence lifetime) after only short exposure of the analyte detecting member to the sample. It was discovered through modeling that the analyte detecting member had in fact "used up" all the glucose in the sample solution, and the volume of the sample was subsequently increased.

The discussion of the various optima for the analyte detecting member and their derivation from the model are beyond the scope of this paper and will be reported elsewhere. However, based on multiple model runs and their experimental verification, we have assembled a number of qualitative design rules that should be generally applicable.

The thickness of the whole blood sample layer has no significant effect unless sample layer is very thin (<100 micrometers) and is not shielded from the atmosphere.

In one embodimetn, a thinner analyte detecting member will be faster, but oxygen diffusion from the sample will start to be noticeable for analyte detecting members thinner than 100 micrometers. A higher GOX concentration can compensate for this effect. Oxygen or glucose-controlled GOX behavior is not a function of layer thickness but of the ratio between hydrophilic and hydrophobic volume and GOX concentration.

GOX concentration has to be balanced with the hydrophobic phase volume fraction to ensure a good dynamic range as well as a glucose-controlled reaction mechanism.

A ratio of hydrophilic to hydrophobic phase of 80/20 is ideal, but this can be modified as long as GOX concentration is modified as well. Increasing the ratio has three effects that beneficially enhance each other and decrease analyte detecting member response time: (a) faster diffusion of glucose in the hydrophilic phase (there is less impenetrable hydrophobic material in the way), (b) faster removal of oxygen from the hydrophobic phase (because there is less stored oxygen available), and (c) a higher amount of GOX can be used, because there is more hydrophilic phase.

Both layer thickness as well as the ratio of hydrophilic to hydrophobic phase will impact the overall fluorescence intensity that can be obtained form the analyte detecting member.

A low hydrogel polymer fraction (a higher water content) in the hydrogel yelds analyte detecting members with faster response.

Catalase contamination in the hydrogel layer converts hydrogen peroxide back into oxygen, thus removing half of the oxygen-consuming effect that the consumption of glucose had on the hydrophobic layer. GOX with low catalase contamination is required.

Droplet sizes below 5 micrometers ensure oxygen diffusion inside the droplets is not a controlling parameter.

In summary, we have found that an exclusively experimental approach of "build & test" is usually not preferable for microscale diagnostic device development, because nano-scale analyte detecting members for prototype testing are not generally available. The right combination of prototype modeling and testing is desired for the rapid development of microanalytical devices for in-vitro diagnostic testing.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, with any of the above embodiments, the location of the penetrating member drive device may be varied, relative to the penetrating members or the cartridge. The method may be used to design analyte detecting member for use with a variety of devices and is not limited to the lancing devices referenced herein. With any of the above embodiments, the penetrating member tips may be uncovered during actuation (i.e. penetrating members do not pierce the penetrating member enclosure or protective foil during launch). With any of the above embodiments, the penetrating members may be a bare penetrating member during launch. With any of the above embodiments, the penetrating members may be bare penetrating members prior to launch as this may allow for significantly tighter densities of penetrating members. In some embodiments, the penetrating members may be bent, curved, textured, shaped, or otherwise treated at a proximal end or area to facilitate handling by an actuator. The penetrating member may be configured to have a notch or groove to facilitate coupling to a gripper. The notch or groove may be formed along an elongate portion of the penetrating member. With any of the above embodiments, the cavity may be on the bottom or the top of the cartridge, with the gripper on the other side. In some embodiments, analyte detecting members may be printed on the top, bottom, or side of the cavities. The front end of the cartridge maybe in contact with a user during lancing. The same driver may be used for advancing and retraction of the penetrating member. The penetrating member may have a diameters and length suitable for obtaining the blood volumes described herein. The penetrating member driver may also be in substantially the same plane as the cartridge. The driver

may use a through hole or other opening to engage a proximal end of a penetrating member to actuate the penetrating member along a path into and out of the tissue.

The publications discussed or cited herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed. All publications mentioned herein are incorporated herein by reference to disclose and describe the structures and/or methods in connection with which the publications are cited.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

Expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

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WHAT IS CLAIMED IS:

1. A method for designing an analyte detecting member, the method comprising:

(a) mathematically replicateing the significant physical and chemical processes taking place in the analyte detecting member and sample;

(b) dividing assay time into small time steps and the analyte detecting member into small control volumes, wherein during each time step (and in each control volume), the model simultaneously solves a specie conservation equation for each important constituent: oxygen, glucose, glucose oxidase, catalase, and hydrogen peroxide.

2. The method of claim 1 wherein each conservation equation includes an accumulation term, a diffusion term, and a production/destruction term wherein the latter relies on a production rate calculated either as a Michaelis-Menton reaction (catalase) or Ping-Pong Bi-Bi reaction (glucose oxidase).

3. The method of claim 1 wherein tracking the diffusion of each important chemical component of the emulsion and sample, the chemical reactions between them, and the resulting signal from oxygen depletion.

4. The method of claim 1 wherein treating the emulsion as a continuum with properties based on volume-fraction averages of the properties of the hydrophobic and hydrophilic phases.

ABSTRACT OF THE DISCLOSURE

In one embodiment, the invention disclosed here comprises the use of a mathematical modeling algorithm to develop a list of design rules for dispersed-phase-based biosensors. Furthermore, various pieces of hardware as well as embodiments of a glucose sensor are disclosed.

Figures:

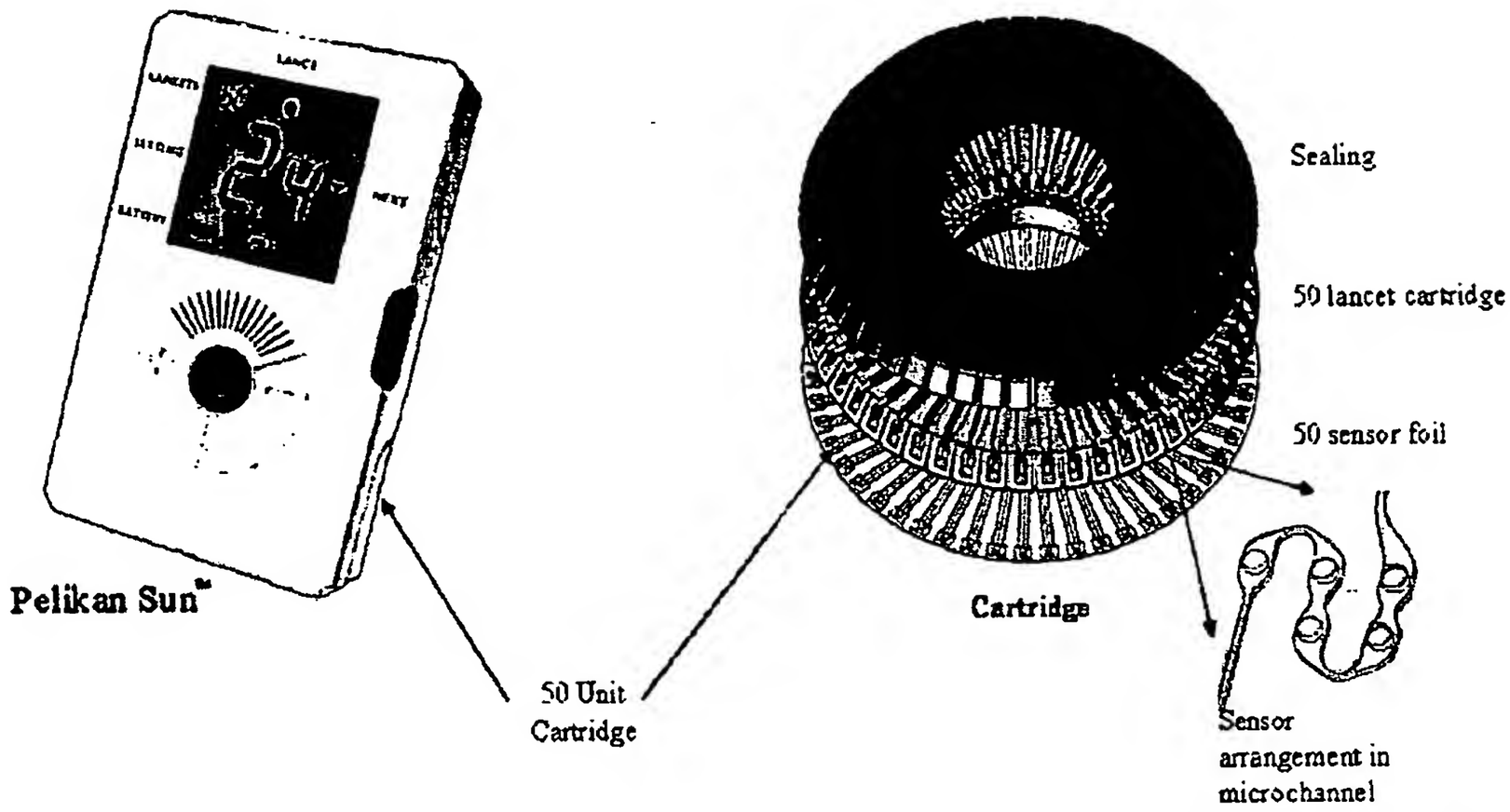


Figure 1 - prototype sensor arrangement and integrated lancing and blood testing device.

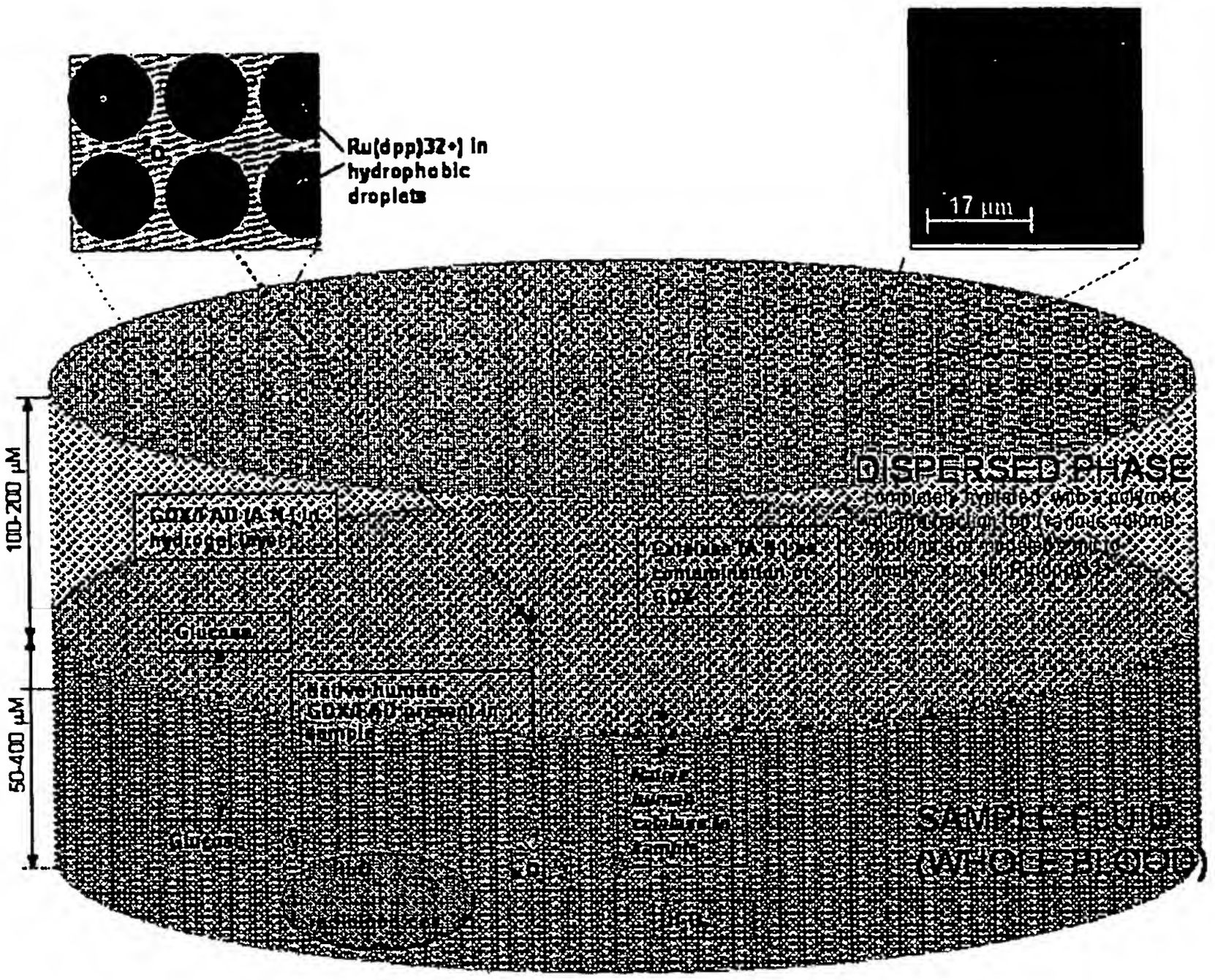


Figure 2 – The sensor as modeled after initial contact of sensor and sample. The embedded photo shows a close-up of the sensor membrane with the emulsion of hydrophobic microdroplets dispersed in hydrophilic phase. Photo courtesy University of Virginia.

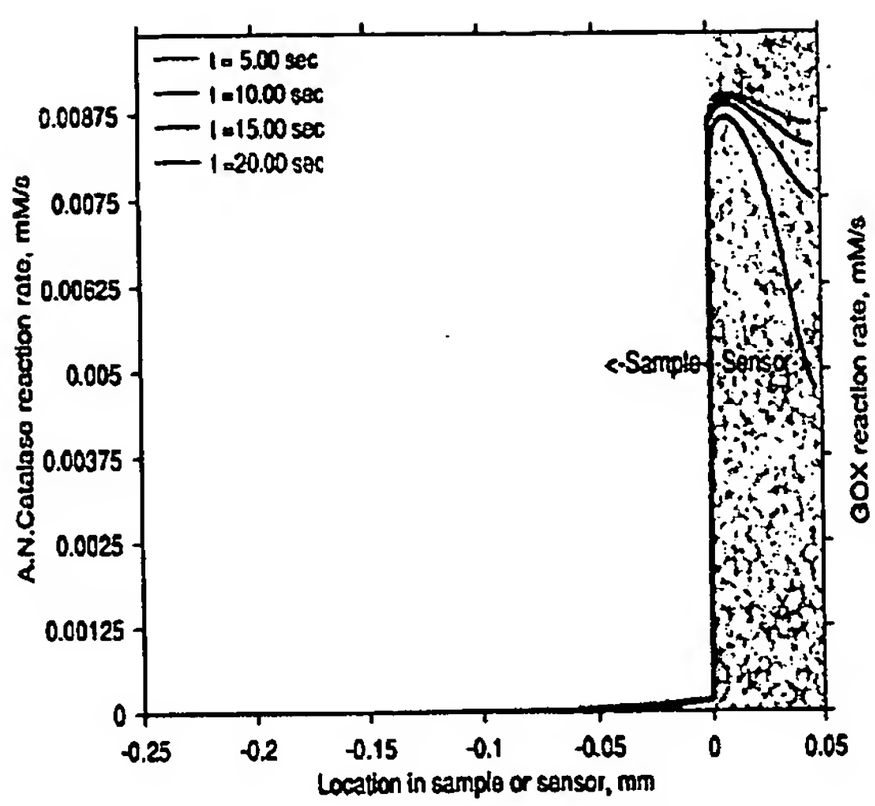


Figure 3a

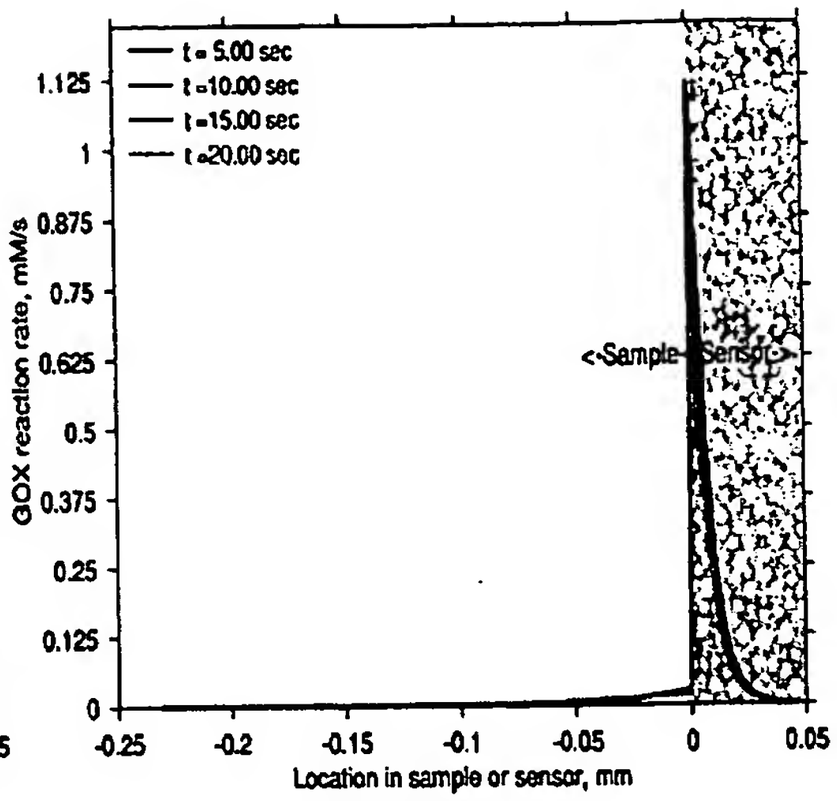


Figure 3b

Figure 3 - Reaction rates of enzyme reactions on the sample-sensor interface.

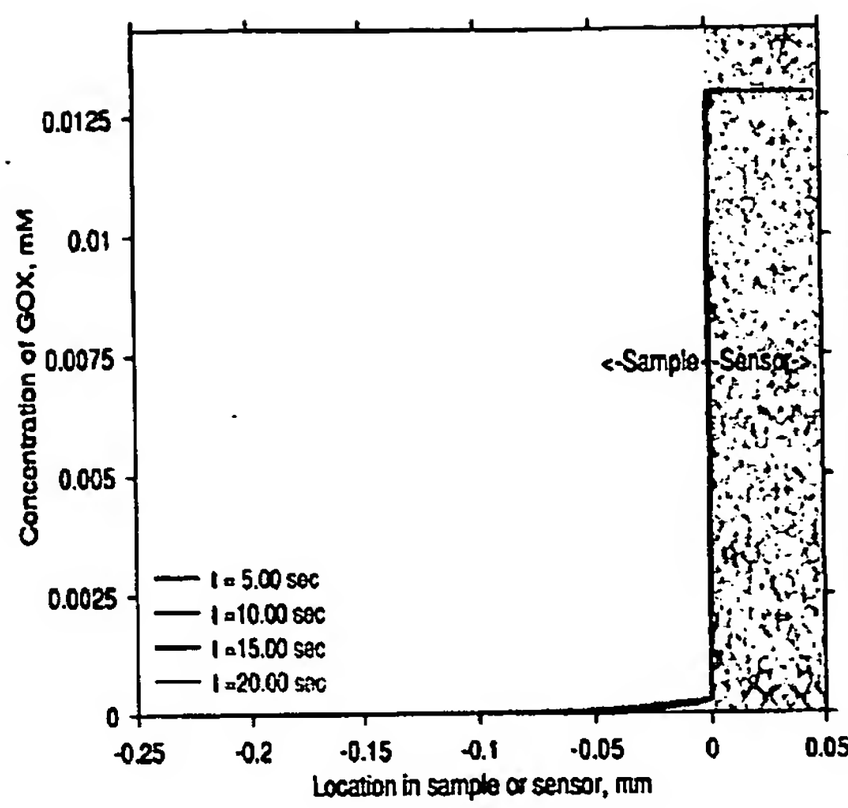


Figure 4a

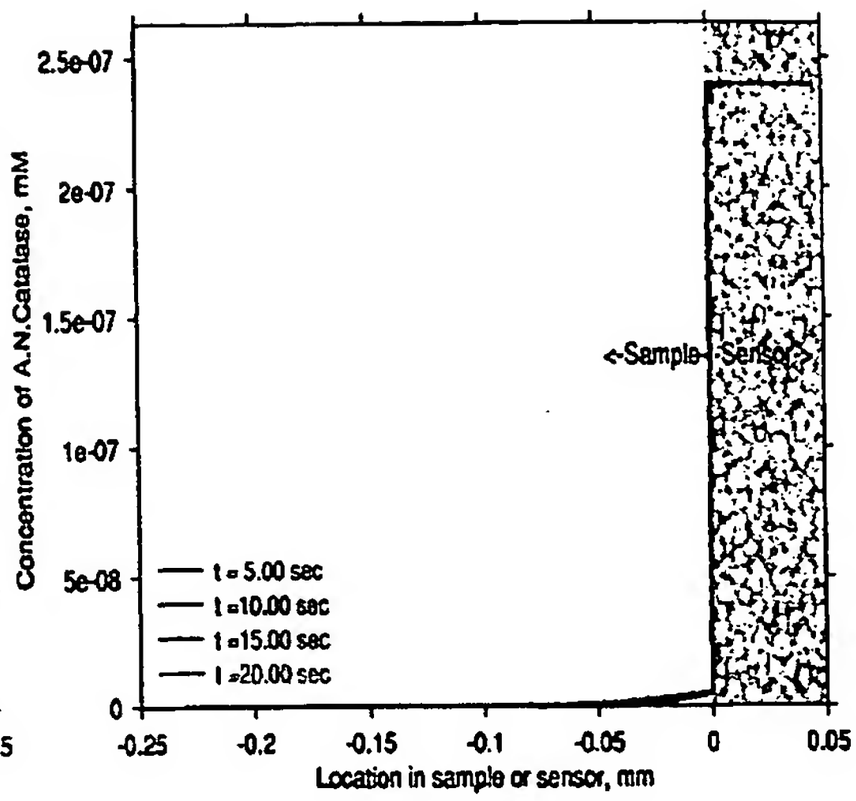


Figure 4b

Figure 4 - Concentrations profile of enzymes along the sample-sensor interface

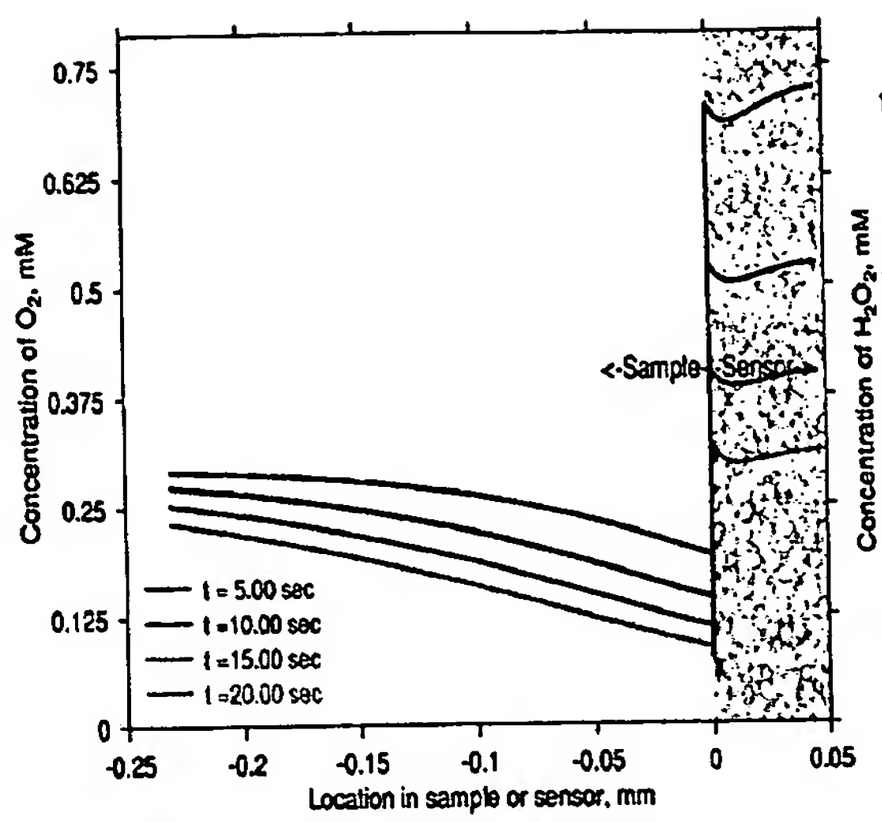


Figure 5a

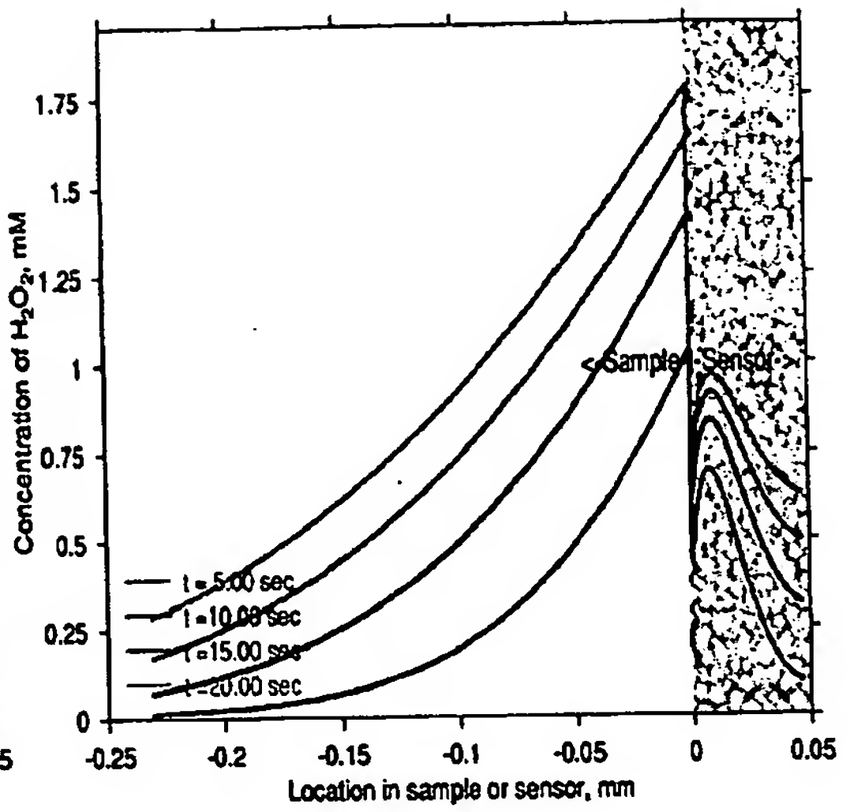


Figure 5b

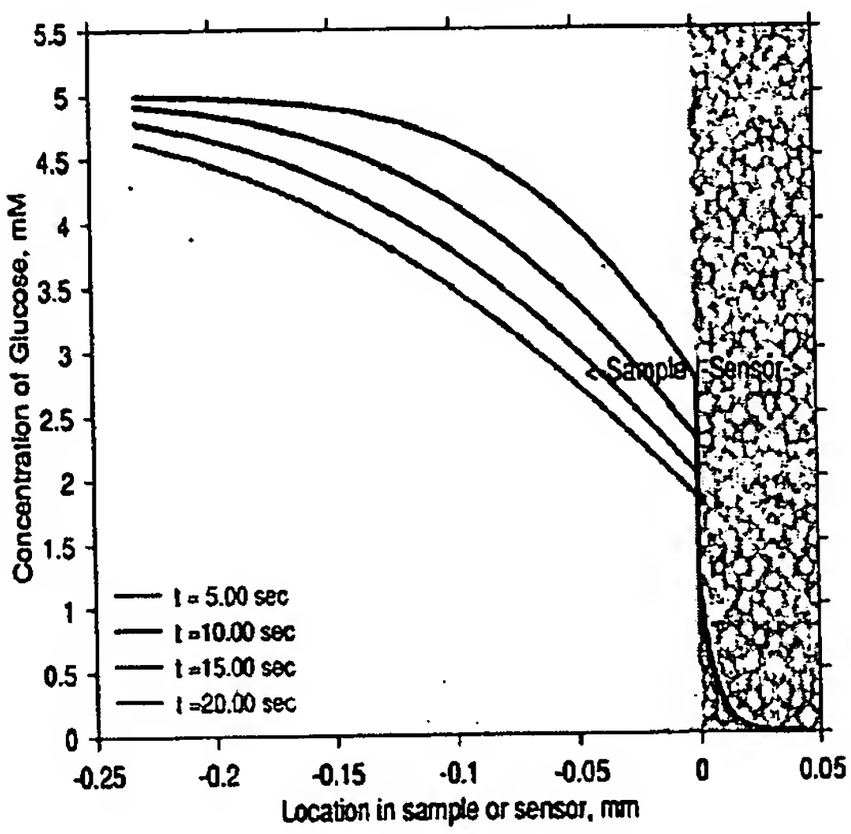


Figure 5c

Figure 5 - Concentrations of reactants along the sample-sensor interface

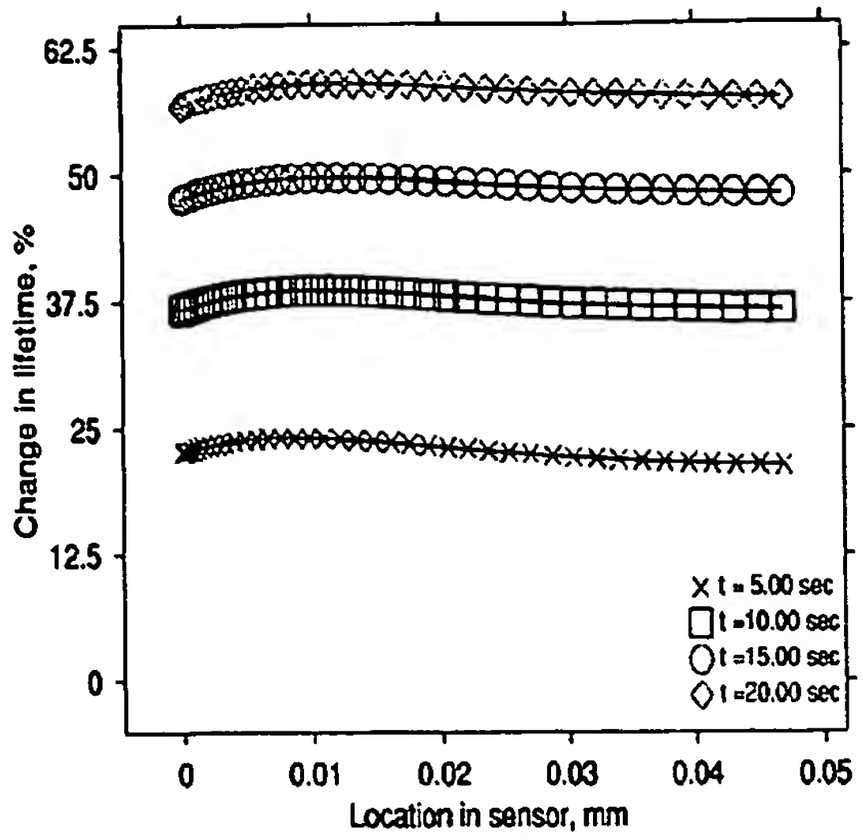


Figure 6 - Change in Fluorescence lifetime as a function of sensor response to glucose

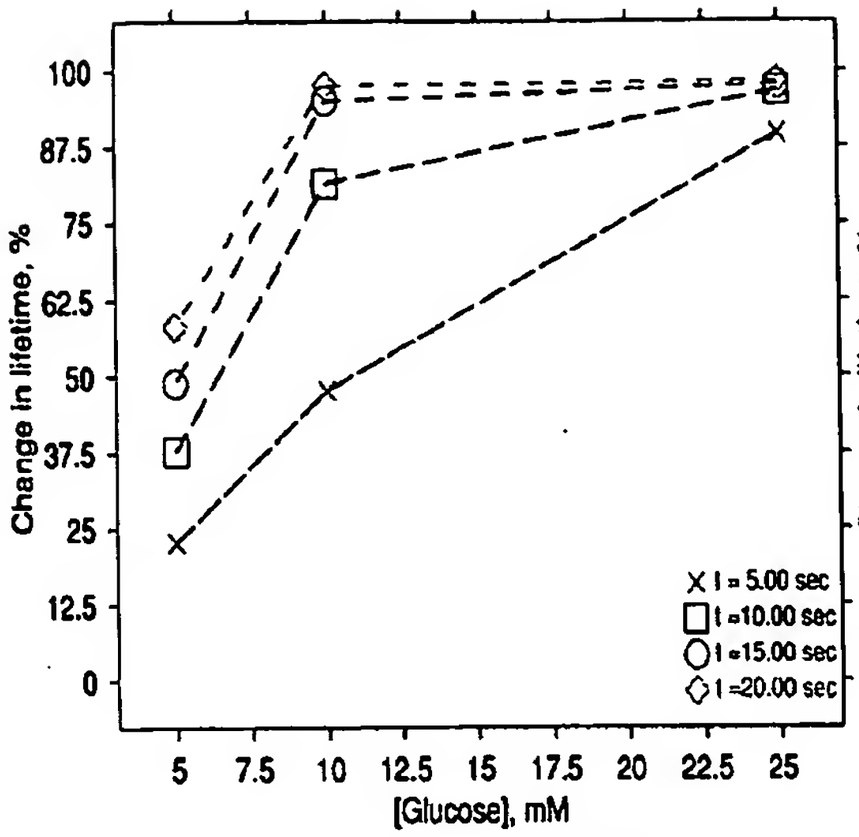


Figure 7a

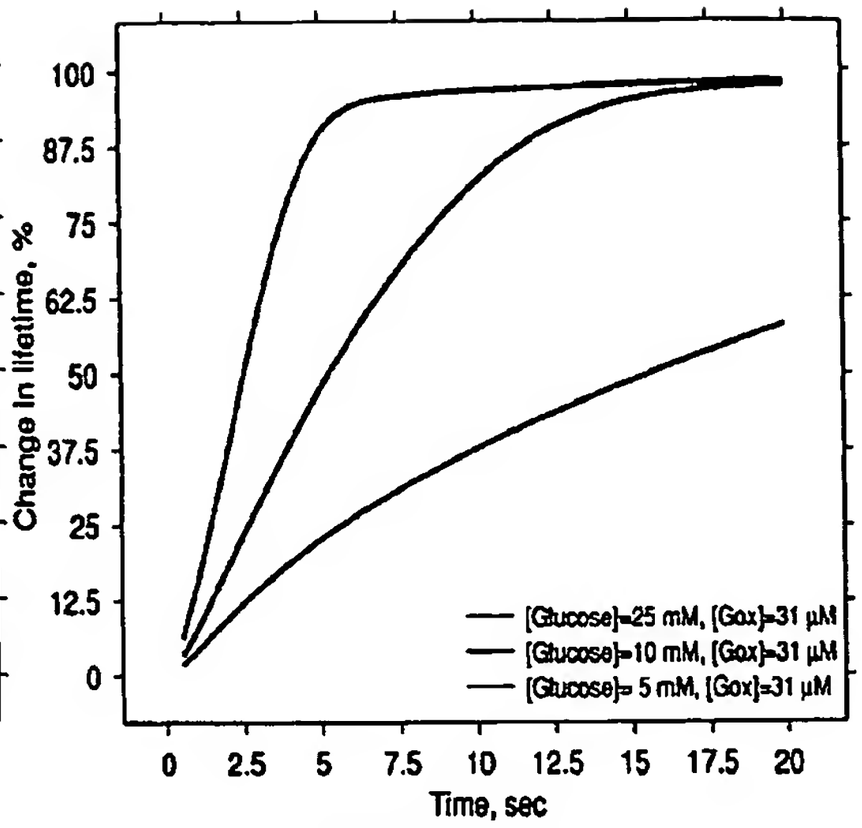
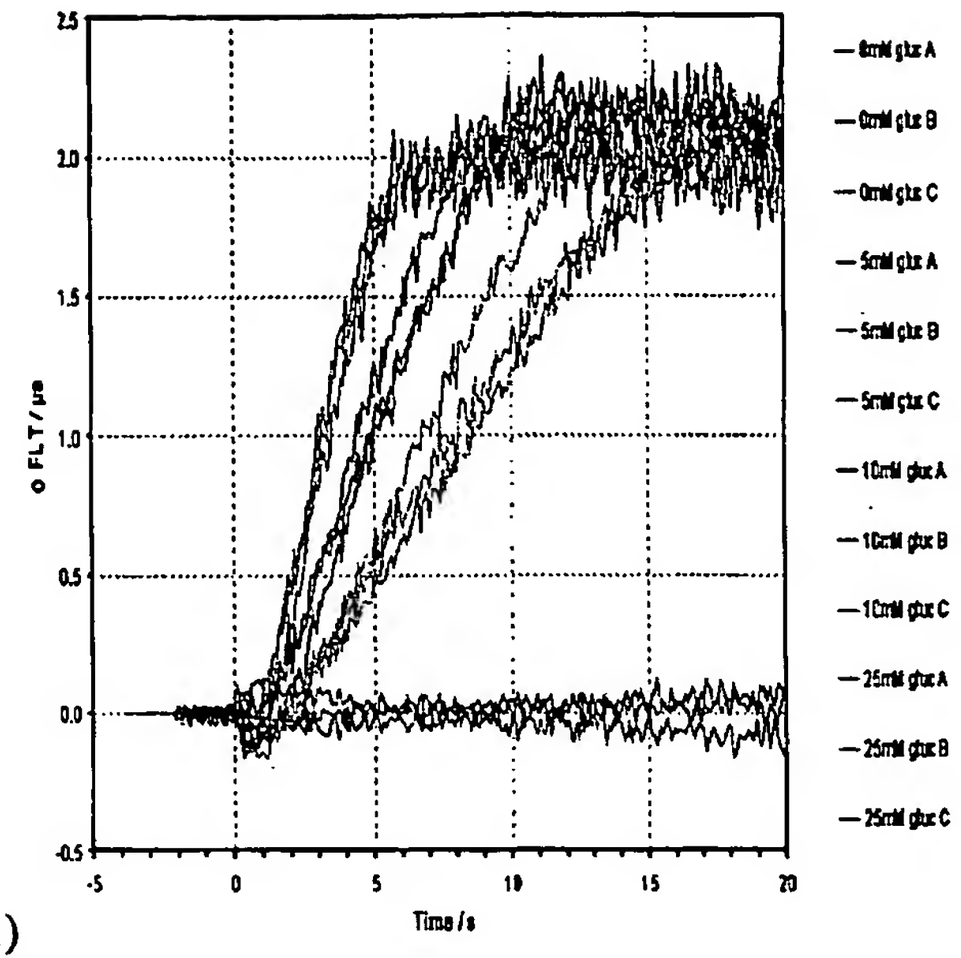


Figure 7b

Figures 7 - Simulated dynamic calibration (7a) and response (7b) graphs of modeled glucose sensor



1)

1.Figure 8: Experimentally obtained response curve of a sensor designed according to the sensor model predictions shown above. Graph courtesy Cranfield University.

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